Endogenous opioid signalling in the brain during pregnancy and lactation

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Abstract

During pregnancy, the regulation of several neuroendocrine systems are altered to support the pregnancy and facilitate the transition to motherhood. These adaptations are organised by the mother's brain and include those that serve to optimise fetal growth, protect the fetus(es) from adverse prenatal programming by maternal stress, facilitate timely parturition and ensure the offspring are nourished and cared for after birth. Although pregnancy hormones are important in inducing and maintaining many of these adaptations, their effects are often mediated via interactions with neuropeptide systems in the brain. In particular, endogenous opioids in the maternal brain play key roles in altered regulation of the stress axis, the oxytocin system, the prolactin system and in the neural circuits controlling maternal behaviour. Together these adaptations maximise the likelihood of a successful pregnancy outcome.

Introduction

During pregnancy altered neuropeptide signalling in the maternal brain allows physiological adaptations that maximise the likelihood of a successful pregnancy outcome. Several neuroendocrine systems are modified in pregnancy. For example, oxytocin stores in the posterior pituitary are enlarged so there are sufficient reserves to meet the demand at parturition and during lactation. At the same time oxytocin neurones have to be kept in check to prevent premature activation and minimise the risk of preterm birth. Exposure of the developing fetus to maternal stress hormones can lead to intra-uterine growth restriction and have long term adverse effects on the fetal brain, hence maternal stress responses are restrained in pregnancy to conserve energy and protect the fetus. The central control of prolactin secretion is altered so a state of hyperprolactinemia can develop to support milk production and secretion, to sustain lactation and nourish the offspring. To facilitate the transition to motherhood, the neural circuits governing maternal behaviour are primed to ensure the rapid expression of appropriate maternal care after birth. These adaptations are driven primarily by the actions of pregnancy hormones on the brain; however endogenous opioid mechanisms play important regulatory roles in these systems. Here, focussing on the rodent literature, we consider the contribution of endogenous opioids in mediating critical changes in the maternal brain that support the pregnancy, prepare females for birth and motherhood.

Endogenous opioids

There are three families of endogenous opioids: the enkephalins, dynorphins and endorphins, each derived from different precursors: proenkephalin (pENK), prodynorphin (pDYN) and proopiomelanocortin (POMC), respectively (Drolet et al. 2001) and three main types of opioid receptor, referred to as mu (μ), delta (δ) and kappa (κ)(Mansour et al. 1994a). Enkephalins bind to μ- and δ-receptors, dynorphins to κ-receptors and endorphins to μ- and κ- receptors (Russell and Douglas 2000). Endogenous opioids and their receptors are widely distributed throughout the CNS (Le Merrer et al. 2009) where they play an important role in regulating responses to stress, modulating pain, mood and emotionality, food intake, reward and attachment (Bali et al. 2015; Benarroch 2012; Bodnar 2011; Drolet et al. 2001). During pregnancy, endogenous opioids play key roles in promoting adaptations in the maternal brain, particularly in the arcuate, paraventricular and supraoptic nuclei (Fig. 1), that ultimately serve to maximise the likelihood of a successful pregnancy outcome.

The HPA axis

The hypothalamo-pituitary-adrenal (HPA) axis is the major neuroendocrine system which responds to stress. Stress exposure results in activation of a population of neurosecretory neurones in the parvocellular region of the paraventricular nucleus (pPVN) in the hypothalamus which synthesise two neuropeptides: corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH and AVP are released from nerve terminals at the median eminence into the hypophysial portal blood system and act synergistically on anterior pituitary corticotrophs to stimulate ACTH secretion, which in turn triggers secretion of glucocorticoids from the adrenal cortex. Glucocorticoids play a vital role in restoring homeostasis in the face of stress by mediating appropriate behavioural and metabolic adaptations and also switch off the HPA axis, via a negative feedback loop, when the stress no longer poses a threat.

Attenuated HPA axis responses in pregnancy

In late pregnant rodents, the HPA axis is less responsive to a host of psychological and physical stressors, such as exposure to a novel environment, air-puff, the elevated plus maze, noise, social stress, forced swimming, immune challenge, as well as to stimulation by metabolic peptides or CRH; and this hyporesponsive state is maintained through parturition and lactation, until weaning (Brunton et al. 2006a; Brunton et al. 2005; Brunton and Russell 2003; Brunton and Russell 2010; da Costa et al. 1997; Douglas et al. 2003; Ma et al. 2005; Neumann et al. 2003; Neumann et al. 1998; Shanks et al. 1999; Toufexis et al. 1999; Windle et al. 1997). Hence, stress-induced ACTH and corticosterone secretion is markedly reduced or completely suppressed in late pregnancy and during lactation, as a result of adaptations at the level of both the anterior pituitary and the brain, though those in the hypothalamus seem to be of key importance (Brunton 2010). For example, stress is less effective in activating the parvocellular CRH/AVP neurones in the PVN, meaning activity of the HPA axis is restrained at the apex of the system (Brunton et al. 2005; da Costa et al. 2001; da Costa et al. 1996; Lightman and Young 1989). Importantly, this phenomenon of reduced glucocorticoid responses to stress is also observed in pregnant women (Kammerer et al. 2002; Schulte et al. 1990). It is thought that attenuated HPA axis responses to stress in pregnancy function to conserve energy supplies for

the pregnancy and minimise exposure of the fetus(es) to excessive levels of maternal glucocorticoids, which can have long-term adverse programming effects (Maccari et al. 2014).

Endogenous opioids and regulation of the HPA axis

Opioid synthesising neurones are present in stress-related regions of the brain including the cerebral cortex, amygdala, lateral septum, bed nucleus of the stria terminalis (BNST), preoptic area, hypothalamus, nucleus tractus solitarii (NTS) and ventrolateral medulla (VLM) (Harlan et al. 1987; Khachaturian et al. 1983). Several studies provide evidence for endogenous opioids in modulating behavioural and HPA axis responses to stress (Barfield et al. 2010; Brunton et al. 2005; Buckingham and Cooper 1986; Buller et al. 2005; Douglas et al. 1998a; Drolet et al. 2001; Grisel et al. 2008; Sanders et al. 2005) and acute stress results in an increase in gene expression for enkephalin in brain regions involved in stress processing, including the PVN and the brainstem (Ceccatelli and Orazzo 1993; Harbuz et al. 1994; Harbuz and Lightman 1989; Mansi et al. 2000). The effects of endogenous opioids in the brain on stress-related behaviours and neuroendocrine stress responses are complex, and region- and opioid receptor type-dependent. For example, there is evidence that endogenous endorphins and enkephalins aid stress-coping, particularly under chronic stress conditions, and have anxiolytic actions, whereas dynorphin has been demonstrated to have anxiogenic actions (Barfield et al. 2010; Berube et al. 2013; Berube et al. 2014; Grisel et al. 2008; Henry et al. 2018; Kang et al. 2000; Katoh et al. 1990; Konig et al. 1996), though these effects depend on the site of action in the brain.

In male rats (and non-pregnant females), administration of an exogenous opioid receptor agonist (e.g. morphine) results in enhanced, while an opioid receptor antagonist (naloxone) suppresses HPA axis responses to acute stress (Buckingham and Cooper 1984, 1986; Buller et al. 2005). This is evidently the result of a central action, as morphine, met-enkephalin and leu-enkephalin stimulate CRH secretion from hypothalamic preparations, but not ACTH release from the pituitary (Buckingham and Cooper 1984) and centrally administered naloxone reduces stress-induced activation of CRH neurones in the pPVN (Buller et al. 2005). However in pregnancy, endogenous opioids switch to having a net inhibitory role over HPA axis function.

Endogenous opioids and HPA axis regulation during late pregnancy and parturition

Attenuated HPA axis responses to stress in pregnancy are a consequence of the emergence of a central inhibitory opioid mechanism. Hence, systemic administration of naloxone reinstates HPA axis responses to stressful stimuli, such as forced swimming and immune challenge in late pregnant rats (Brunton et al. 2005; Douglas et al. 1998a) and to parturition-related stimuli at birth (Wigger et al. 1999), reflected by increased ACTH and corticosterone secretion, together with increased activation of pPVN neurones and increased gene expression for *Crh* in the pPVN (Brunton et al. 2005).

In late pregnancy, gene expression for pENK-A (*Penk*) and μ–opioid receptor (MOR; *Oprm1*) are up-regulated in the NTS of the brainstem and *Pomc* mRNA and β-endorphin immunoreactivity is increased in the arcuate nucleus compared with non-pregnant rats (Brunton et al. 2005; Douglas et al. 2002). However, it is likely that the NTS is the source of the opioids that are involved in restraining HPA axis responses in late pregnant rats, at least for those stressors where activation of the CRH neurones is mediated via brainstem afferents. The evidence is as follows: immune challenge with the cytokine, interleukin-1β (IL-1β) activates hypothalamic-projecting noradrenergic neurones in the A2 region of the NTS. This results in increased noradrenaline release from nerve terminals in the PVN which stimulates CRH neurones and hence ACTH and corticosterone secretion. In late pregnancy, despite similar activation of the NTS neurones, systemic IL-1β fails to result in increased noradrenaline release in the PVN. Similarly, noradrenaline release in the PVN evoked by forced swim stress is significantly lower in late pregnant rats compared with virgin females (Douglas et al. 1995). Naloxone infused directly into the PVN restores IL-1β-induced noradrenaline release in the PVN (Brunton et al. 2005), indicating that endogenous opioids act presynaptically on noradrenergic inputs to the PVN to inhibit evoked noradrenaline release. If the noradrenergic NTS neurones are the same population that display increased gene expression for MORs and enkephalin in pregnancy, this would provide a mechanism whereby endogenous opioids (i.e. enkephalin) act on up-regulated presynaptic MORs on noradrenergic nerve terminals to auto-inhibit noradrenaline release in the PVN (Fig. 2), hence reducing stimulation of the CRH neurones in late pregnancy (Brunton et al. 2005). The same mechanism is hypothesised to limit activation of the magnocellular oxytocin neurones in late pregnancy (see below)(Brunton et al. 2006b; Leng et al. 1995).

A reduction in the effectiveness of the noradrenergic input to the pPVN CRH neurones has also been implicated in underlying reduced HPA axis responses to stress during lactation (Toufexis et al. 1998; Toufexis and Walker 1996), however the precise mechanisms are not known. However, in contrast to pregnancy and parturition, HPA axis hyporesponsiveness during lactation is dependent upon the

suckling stimulus provided by the pups (Lightman and Young 1989) and is likely to involve central prolactin actions (Torner and Neumann 2002; Torner et al. 2002).

Oxytocin

Oxytocin is synthesised by magnocellular neurones in the PVN and the supraoptic nuclei (SON), whose axons project to the posterior pituitary gland (Russell and Brunton 2009). Upon activation, oxytocin is secreted from the nerve terminals in the posterior pituitary into the systemic circulation. Oxytocin plays an important role in promoting uterine contractions during at birth and is vital in stimulating milk ejection during lactation (for review see (Burbach 2006)). Oxytocin is also released within the brain from the dendrites of the magnocellular neurones and also from the terminals of centrally projecting neurones, where it plays an important role in promoting the expression of maternal behaviour after birth (Knobloch et al. 2012; Lee et al. 2009; Ludwig and Leng 2006; Pedersen et al. 1994). In the rat, oxytocin is also considered to be a 'stress hormone'; hence stress exposure activates oxytocin neurones (reflected by increased expression of the protein product of the immediate early gene, c-fos) and stimulates oxytocin secretion (Brunton et al. 2006b; Douglas et al. 2000; Lang et al. 1983).

During pregnancy, the oxytocin neurones are maintained in a quiescent state that limits oxytocin secretion and permits the accumulation of oxytocin stores in the posterior pituitary (which expand by around 75% in rats) (Douglas et al. 1993b; Fuchs and Saito 1971), for when it is required at parturition and subsequent lactation. Accruing these stores is important as oxytocin synthesis is evidently not increased in pregnancy (Douglas et al. 1998b). Critically, limiting activity of the oxytocin neurones in pregnancy also minimises the likelihood of premature oxytocin secretion that could lead to uterine contractions and preterm birth (Elovitz and Mrinalini 2004; Goodwin et al. 1994). There are several mechanisms that contribute to restraining oxytocin secretion during pregnancy (Brunton et al. 2013). These include auto-inhibition by nitric oxide (Srisawat et al. 2000) and the potentiating effects of allopregnanolone on GABA actions at $GABA_A$ receptors (Brussaard and Herbison 2000), however here the focus is on endogenous opioid mechanisms.

Oxytocin and Parturition

A2 noradrenergic neurones in the NTS of the brainstem project to magnocellular oxytocin neurones in the SON and PVN (Ericsson et al. 1994; Meddle et al. 2000) . At parturition, noradrenaline release is increased in the SON and PVN and acts on α1 adrenoceptors to activate the oxytocin neurones (Douglas et al. 1998b; Douglas et al. 2001; Herbison et al. 1997; Meddle et al. 2000; Randle et al. 1986). Activated oxytocin neurones fire in synchronised bursts, secreting pulses of oxytocin into the blood which acts on myometrium oxytocin receptors (OTR), up-regulated by increased levels of estradiol acting on estrogen receptor-α (ERα) (Mesiano et al. 2002; Murata et al. 2000; Murata et al. 2003; Welsh et al. 2012), to stimulate uterine contractions. Signals from the contracting uterus and distended birth canal are relayed by spinal and vagal afferents (Higuchi et al. 1986; Peters et al. 1987) to the A2 noradrenergic NTS neurones, resulting in a positive feedback loop which drives further oxytocin release, known as the Ferguson reflex (Ferguson 1941). Oxytocin release from the dendrites of activated magnocellular neurones acts locally to synchronise burst firing of the oxytocin neurones, necessary for pulsatile oxytocin secretion at parturition and during milk-ejection (Dyball and Leng 1986; Moos et al. 1998; Rossoni et al. 2008).

Endogenous opioids and control of oxytocin secretion

Oxytocin secretion is restrained by endogenous opioids. Opioids act both centrally, on the oxytocin neurones or their inputs, as well as on axon terminals in the posterior pituitary (Bicknell et al. 1988; Zhao et al. 1988a, b). In non-pregnant rats and during early pregnancy, endogenous opioids acting via κ-opioid receptors on axon terminals in the posterior pituitary inhibit oxytocin secretion and this is the principal mechanism involved in regulating oxytocin secretion (Douglas et al. 1993b; Leng et al. 1994). However, during the last week of pregnancy, a κ-agonist is less effective in inhibiting electrically stimulated oxytocin release from isolated neural lobes, indicating a desensitisation of this inhibitory opioid mechanism in the pituitary (Douglas et al. 1993b), allowing for enhanced oxytocin secretion at parturition in response to excitation of the oxytocin cell bodies. At this time a central inhibitory opioid system becomes activated (described below), and this mechanism predominates in restraining activity of the oxytocin neurones in response to excitatory stimuli in late pregnancy (Douglas et al. 1993b; Douglas et al. 1995).

Stress-induced oxytocin responses in pregnancy

In non-pregnant rats, in addition to activating the HPA axis, systemic IL-1β also activates oxytocin neurones, increasing their firing rate and resulting in increased oxytocin secretion into the blood (Brunton et al. 2012; Brunton et al. 2006b). In contrast, IL-1β has no effect on the electrical or secretory activity of oxytocin neurones in late pregnant rats (Brunton et al. 2012; Brunton et al. 2006b). This is the result of a central endogenous opioid mechanism, since naloxone increases the firing rate of oxytocin neurones and unmasks a much exaggerated oxytocin secretory response to IL-1β and in late pregnant rats (Brunton et al. 2006b). A similar response is seen following forced swimming or CCK administration, where oxytocin secretion, Fos induction in the SON neurones and the firing rate of oxytocin neurones in the SON is potentiated by naloxone to a far greater extent in late pregnant rats compared with virgin females (Douglas et al. 1998a; Douglas et al. 1995). Forced swimming, CCK and IL-1β mediate their excitatory effect on oxytocin neurones via noradrenergic neurones in the NTS. As mentioned above, in late pregnancy these stimuli fail to trigger noradrenaline release in the PVN (Brunton et al. 2005; Douglas et al. 2005). It is proposed that the same endogenous opioid mechanism that prevents excitation of the CRH neurones in the PVN (described above) by inhibiting noradrenaline release from afferent inputs to the PVN (mediated by enkephalin actions on presynaptic MORs) also serves to keep the oxytocin neurones in the SON and PVN under control in late pregnancy (Fig. 2). Given that A2 noradrenergic NTS neurones also relay stimuli from the birth canal to drive oxytocin secretion at parturition, it is hypothesised that maintaining quiescence of this pathway during pregnancy plays an important role in preventing premature activation of the oxytocin neurones and ensuring birth is not triggered prematurely.

While this inhibitory opioid mechanism is anticipated to prevent inappropriate activation of the oxytocin neurones by stimuli such as stress in late pregnancy, central opioid inhibition of the oxytocin neurones persists during parturition (Leng et al. 1988; Neumann et al. 1991), but is withdrawn soon after birth (Leng et al. 1988) and is not detected in lactation (Douglas et al. 1993b; Neumann et al. 1993). μ- and κ-receptor agonists inhibit the electrical activity of oxytocin neurones, inhibit oxytocin secretion and delay established parturition (Bicknell et al. 1988; Douglas et al. 1993a; Leng et al. 1988; Pumford et al. 1991; Pumford et al. 1993; Russell et al. 1989). Conversely naloxone administration during parturition increases oxytocin secretion and reduces the interval between pup births (Leng et al. 1988). Similarly, naloxone can prevent the reduction in oxytocin secretion and the interruption to parturition induced by stress (Leng et al. 1988). Together these data indicate potent opioid inhibition over oxytocin neurones at parturition, which may serve to regulate the timing of births so inter-birth intervals are optimal to allow for appropriate maternal behaviour between deliveries.

Endogenous opioids also restrain oxytocin release within the SON and PVN in late pregnancy, however this mechanism is down-regulated at parturition (Douglas et al. 1995; Neumann et al. 1993). Given local oxytocin release within the magnocellular nuclei plays an important role in positive feedback regulation of oxytocin neuronal activity (Neumann et al. 1996), withdrawal of this opioid inhibition permits potent excitation of the oxytocin neurones and promotes synchronised burst firing of oxytocin neurones during parturition and suckling for effective uterine contractions and milk ejection.

Induction of inhibitory endogenous opioid tone over HPA axis and oxytocin responses in pregnancy

The endogenous opioid mechanism that restrains activity of the HPA axis and magnocellular oxytocin system in pregnancy is induced by the neuroactive metabolite of progesterone, allopregnanolone (Brunton et al. 2012; Brunton et al. 2009). Allopregnanolone concentrations progressively increase in the blood and in the brain during pregnancy (Concas et al. 1998). In the brain, allopregnanolone concentrations reach maximal levels in late pregnancy, before declining dramatically before parturition (Concas et al. 1998). Gene expression for 5α-reductase (*Srd5a*) and 3α-hydroxysteroid dehydrogenase (*Akr1c4)*, the enzymes responsible for the conversion of progesterone to dihydroprogesterone and then allopregnanolone, are up-regulated in the NTS in late pregnancy (Brunton et al. 2009) and activity of these enzymes is also increased in the hypothalamus of late pregnant rats (Brunton et al. 2009); presumably leading to increased local allopregnanolone synthesis. Blocking allopregnanolone synthesis in pregnant rats with the 5α-reductase inhibitor, finasteride, not only restores ACTH and oxytocin secretory responses to immune challenge, but reduces *Penk* gene expression in the NTS to levels similar to those found in non-pregnant animals (Brunton et al. 2012; Brunton et al. 2009). Moreover, administration of allopregnanolone to virgin rats (to simulate pregnancy levels) rapidly up-regulates *Penk* gene expression in the NTS to levels equivalent to those observed in late gestation and induces opioid inhibition over stress-induced ACTH and oxytocin secretion (Brunton et al. 2012; Brunton et al. 2009). Hence, increased concentrations of allopregnanolone in the NTS in pregnancy evidently induce and maintain an inhibitory opioid mechanism that tightly controls both the oxytocin and the CRH neurones. This is important since inhibiting 5α-reductase activity (and hence allopregnanolone production) during the last week of gestation leads to preterm birth and increased neonatal mortality (Paris et al. 2011). It remains to be established whether this is a result of premature activation of the oxytocin neurones as a result of withdrawal of endogenous opioid tone or is due to altered GABA signalling to oxytocin neurones, since

allopregnanolone has also been demonstrated to potentiate the inhibitory influence of GABA on oxytocin neurones in late pregnancy (Koksma et al. 2003).

Mimicking pregnancy levels of sex steroids in virgin females with chronic estradiol and progesterone administration induces opioid inhibition over the neurohypophysial oxytocin system, but not the HPA axis (Douglas et al. 2000). Hence naloxone administration potentiates stress-induced oxytocin secretion, but not ACTH or corticosterone in these rats (Douglas et al. 2000). It is unclear why this treatment induces opioid tone over the oxytocin system but not the HPA axis. It is not known whether exogenously administered progesterone is converted to allopregnanolone to exert these effects, though this seems unlikely as this would be expected to result in similar effects on both systems (Brunton et al. 2012; Brunton et al. 2009). Rather, it is possible that the sex steroid treatment expands pituitary stores of oxytocin (as in pregnancy) meaning a greater pool is available for release when opioid restraint is blocked by naloxone.

Central control of prolactin secretion

In non-pregnant animals, prolactin secretion by anterior pituitary lactotrophs is under tonic inhibitory control by dopamine, produced and secreted by hypothalamic tubero-infundibular dopamine (TIDA) neurones in the arcuate nucleus neurones which project to the median eminence and secrete dopamine into the hypothalamo-hypophysial portal blood system (Reymond and Porter 1985). In the anterior pituitary, dopamine acts on D2 receptors expressed on lactotrophs to inhibit prolactin production (Caron et al. 1978; Guillou et al. 2015; Mansour et al. 1990). Prolactin can enter the brain (Walsh et al. 1987); however the process by which it crosses the blood-brain barrier is unclear, although evidently this does not depend upon prolactin receptors (PRL-R) (Brown et al. 2016). Once in the brain, prolactin acts directly on TIDA neurones, which express PRL-Rs, to stimulate activity of the TIDA neurones and up-regulate tyrosine hydroxylase (*Th*; the rate-limiting enzyme in dopamine synthesis) gene expression in TIDA neurones (Arbogast and Voogt 1991; Lerant and Freeman 1998). This results in increased dopamine synthesis and secretion into the portal blood generating a short-loop negative-feedback system whereby prolactin controls its own secretion (Ben-Jonathan et al. 1980).

Prolactin secretion during pregnancy

In the rat, prolactin plays an essential role in preventing regression of the corpus luteum (luteolysis) in early pregnancy, ensuring progesterone secretion to sustain the pregnancy and in preparing the mammary alveoli for milk production (Gibori and Richards 1978; Ormandy et al. 1997). In addition, prolactin (together with estrogen, progesterone and oxytocin) primes the brain to promote maternal behaviour after birth and plays an essential role in lactation by stimulating milk production and secretion (Bridges et al. 1985; Bridges et al. 1990; Bridges and Ronsheim 1990; Lucas et al. 1998; Ormandy et al. 1997). Moreover, increased prolactin in the maternal brain in the perinatal period contributes to restraining basal and stress-induced activity of the HPA axis and oxytocin system (Gustafson et al. 2017; Torner et al. 2002). Accordingly, in pregnancy, there are important adaptations in the hypothalamic mechanisms controlling the prolactin system that must occur in order to facilitate increased prolactin secretion.

In rodents, mating stimulates the onset of twice daily surges in prolactin secretion which persist for the first 8-10 days of pregnancy (Gunnet and Freeman 1983). Around mid-pregnancy, these surges are suppressed when the secretion of placental lactogen begins to increase which acts in a similar fashion to prolactin to stimulate dopamine release from TIDA neurones and thereby inhibit prolactin secretion from the lactotrophs (Demarest et al. 1983a; Lee and Voogt 1999; Smith and Neill 1976; Voogt et al. 1982; Voogt 1984). The night before parturition and following progesterone withdrawal, the TIDA neurones become seemingly insensitive to negative feedback by prolactin and placental lactogen– despite increasing their firing rate, they fail to secrete dopamine in response to prolactin (Anderson et al. 2006a; Romano et al. 2013) and this persists into lactation. This ineffective negative feedback permits a large nocturnal surge in prolactin secretion at the end of pregnancy, facilitating the transition from gestation to motherhood and allowing a state of hyperprolactinemia to develop to sustain lactation (Grattan and Averill 1990; Grattan et al. 2008). The mechanism involved is not fully understood, but is evidently induced by progesterone withdrawal (Grattan and Averill 1990; Soaje et al. 2006) and probably involves changes in prolactin receptor intracellular signalling and reduced TH activity (Anderson et al. 2006a; Anderson et al. 2006b; Steyn et al. 2008). Following parturition, suckling by the pups reduces activity of the TIDA neurones, down-regulates *Th* gene expression and suppresses dopamine release at the median eminence, hence increasing prolactin secretion until weaning when tonic inhibition of prolactin secretion by TIDA neurones is reinstated (Ben-Jonathan et al. 1980; Demarest et al. 1983b; Feher et al. 2010; Selmanoff and Gregerson 1985; Selmanoff and Wise 1981; Wang et al. 1993).

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337 ***Endogenous opioids and regulation of prolactin secretion during pregnancy and lactation***

338

339 Endogenous opioids play a key role in regulating prolactin secretion by the pituitary through actions
340 on TIDA neurones. Endogenous opioid peptides inhibit TIDA neurones and hence dopamine secretion,
341 promoting the prolactin surges in early pregnancy and pre-partum, and suckling-induced prolactin
342 secretion during lactation (Andrews and Grattan 2002, 2003; Callahan et al. 2000; Sagrillo and Voogt
343 1991). Hence, naloxone administration during the night before parturition increases dopamine
344 turnover and inhibits the pre-partum prolactin surge (Andrews and Grattan 2002). Interestingly,
345 treatment with naloxone a couple of days earlier in pregnancy (on day 19) has no effect on prolactin
346 secretion or dopaminergic activity in the mediobasal hypothalamus (Soaje et al. 2006), unless
347 progesterone actions are blocked, which decreases TIDA neurone activity and permits an increase in
348 prolactin secretion (Soaje et al. 2006), supporting the idea that progesterone withdrawal at the end
349 of pregnancy plays a key role in reducing activity of the TIDA neurones and facilitating increased
350 prolactin secretion (Andrews and Grattan 2002; Soaje and Deis 1994). However, on day 19 of
351 pregnancy, despite facilitating increased prolactin secretion, naloxone has no greater effect on the
352 activity of the dopamine neurones than the anti-progesterone given alone (Soaje et al. 2006),
353 suggesting that in addition to the inhibition of TIDA neurones, endogenous opioids may regulate
354 prolactin secretion through another mechanism in the presence of high levels of progesterone,
355 possibly via inhibition of putative prolactin-releasing factor neurones. One such candidate is oxytocin
356 since, oxytocin stimulates prolactin secretion (Gonzalez-Iglesias et al. 2015; Samson et al. 1986) and
357 as described above, oxytocin neurones are inhibited by endogenous opioids in late pregnancy
358 (Brunton et al. 2006b; Douglas et al. 2000). Indeed, recent findings support a role for oxytocin in
359 facilitating prolactin secretion in late pregnancy, but this effect is only apparent when progesterone
360 action is blocked (Villegas-Gabutti et al. 2018).

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362 Immunoreactivity for dynorphin, enkephalins and β-endorphin is present in the arcuate nucleus
363 (Fitzsimmons et al. 1992; Merchenthaler 1994) and contact between opioid peptide-containing nerve
364 terminals and TIDA neurones has been described (Fitzsimmons et al. 1992; Horvath et al. 1992).
365 However, β-endorphin innervation of dopaminergic neurones only represents a small proportion of
366 opioidergic connections in the arcuate nucleus, with the majority expressing dynorphin or enkephalin
367 (Fitzsimmons et al. 1992). During pregnancy and lactation, POMC mRNA expression and β-endorphin
368 immunoreactivity are only modestly increased in the arcuate nucleus in late pregnancy (Douglas et al.

2002), however immunoreactivity and gene expression for enkephalin is markedly up-regulated, such that all TIDA neurones co-express enkephalin (Merchenthaler 1994; Merchenthaler et al. 1995), which is likely driven by increased prolactin (Nahi and Arbogast 2003). Given the lack of *δ*-receptors in the arcuate nucleus (Mansour et al. 1994a; Mansour et al. 1987), it is reasonable to assume that enkephalin released from TIDA neurones acts on μ-opioid receptors in the arcuate nucleus, perhaps in an auto-inhibitory manner (Fig. 3). Indeed, the prolactin surges in early pregnancy, late pregnancy and lactation are inhibited and the activity of TIDA neurones increased, by administration of selective μ- and κ-, but not δ-receptor antagonists (Andrews and Grattan 2003), indicating these receptors play more important roles.

In late pregnancy, in addition to attenuating HPA axis and oxytocin responses to stress, endogenous opioids also restrain stress-induced prolactin secretion (Valdez et al. 2014). This effect is mediated through μ opioid receptors and estradiol and progesterone actions are involved in the induction and maintenance of this inhibitory opioid tone (Valdez et al. 2014). Hence, in pregnancy endogenous opioids, through their inhibitory actions on TIDA neurones, play a key role in permitting a state of hyperprolactinemia which maintains the pregnancy and facilitates lactation. In addition, prolactin actions on the brain also promotes maternal behaviour post-partum (discussed below).

Maternal behaviour

Following the birth of the offspring, maternal behaviour must be expressed swiftly if the young are to be reared successfully. Maternal care consists of a complex set of behaviours including nest-building, retrieving and gathering the young, nursing, grooming and protection from the environment (e.g. cold) and other threats (e.g. unfamiliar conspecifics). The maternal brain is primed for this transition by prolonged exposure to pregnancy levels of ovarian and lactogenic hormones during gestation (for review see (Bridges 2015)).

Neural circuitry and hormonal priming of maternal behaviour

The different elements of maternal behaviour involve distinct, though interconnected circuits in the brain (for review see (Numan 2007)). Of particular importance in the onset and integration of maternal

behavioural responses is the medial preoptic area (mPOA), hence lesions to this region disrupt or abolish maternal behaviour (Cohn and Gerall 1989; Numan et al. 1977; Numan and Smith 1984; Stack et al. 2002; Tsuneoka et al. 2013). Hormone priming mediated by the decline in circulating progesterone at the end of pregnancy, concurrent with increased estradiol activates neurones in the mPOA and induces maternal behaviour (Bridges et al. 1978; Sheehan and Numan 2002) and maternal behaviour can be induced in nulliparous rats treated with sex steroids to mimic the concentrations and pattern of secretion seen in pregnancy (Bridges 1984). Activation of the mPOA and the neighbouring ventral BNST, results in inhibition of neural circuits involving the anterior hypothalamic nucleus and the periaqueductal grey, that normally mediate aversive responses to newborn pups and pup odour in virgin females, thus eliminating avoidance behaviour (Bridges et al. 1999; Numan and Numan 1996; Sukikara et al. 2006); and activation of dopaminergic neurones in the ventral tegmental area (VTA) project to the nucleus accumbens (NAc) to stimulate motivation and reward, making new mothers more responsive to pup-related stimuli (Champagne et al. 2004; Hansen et al. 1991; Keer and Stern 1999; Numan and Smith 1984; Parada et al. 2008; Stolzenberg et al. 2007).

Prolactin and oxytocin also play key roles in stimulating maternal care. Central prolactin infusions stimulate maternal behaviour towards foster pups in steroid-primed virgin rats and prolactin is more effective when administered directly into the MPOA (Bridges et al. 1990); while suppression of endogenous prolactin secretion with bromocriptine delays the onset of maternal behavior (Bridges and Ronsheim 1990). Moreover, a recent study employing conditional PRL-R knockout mice demonstrate prolactin action, specifically in the MPOA, is vital for the normal expression of maternal behavior after birth (Brown et al. 2017). At parturition, oxytocin receptors are up-regulated in several brain regions linked to maternal behaviour, including in the MPOA, BNST and VTA (Meddle et al. 2007; Pedersen et al. 1994). Administration of an oxytocin receptor antagonist into the VTA or the MPOA of parturient impairs maternal behaviour (Pedersen et al. 1994) and central administered exogenous oxytocin is able to induce maternal care in hormonally primed nulliparous rats (Pedersen et al. 1982).

Endogenous opioids and maternal behaviour

At parturition, the withdrawal of up-regulated central endogenous opioid mechanisms, in particular in the mPOA, is necessary to facilitate maternal behaviour (Byrnes and Bridges 2000; Byrnes et al. 2000). Levels of opioids and opioid receptor binding sites in the MPOA are elevated during pregnancy, but decrease in lactation; evidently as a result of changes in ovarian sex steroids (Hammer Jr and

Bridges 1987). Administration of morphine or the μ-receptor agonist, β-endorphin (but not δ or K-receptor agonists), into the MPOA disrupts maternal behaviour in lactating or hormone-primed sensitised virgin rats (Mann and Bridges 1992; Mann et al. 1991; Rubin and Bridges 1984). The role of physiological levels of endogenous opioids in the maternal brain post-partum is unclear, however there is evidence to indicate they may act to regulate nursing bout duration, at least in early lactation (Byrnes et al. 2000) and are involved in regulating the switch from nursing behaviour to predatory/hunting behaviour (Sukikara et al. 2007).

Large scale gene expression studies of the MPOA, medial prefrontal cortex, lateral septum and NAc have identified over 1000 genes/region that are differentially expressed in the maternal brain compared with non-pregnant females (Driessen et al. 2014; Eisinger et al. 2014; Eisinger et al. 2013; Zhao et al. 2014). As well as identifying potential new candidate genes involved in regulating maternal behaviour, studies such as these are paving the way for exploring the networks and interactions between novel genes and the already well-characterised 'maternal' genes. Post-partum dams find pups rewarding (Ferris et al. 2005; Lee et al. 2000), therefore it is particularly interesting that the top 700 of the identified 'maternal genes' are significantly enriched for genes involved in reward and addiction, including genes for the opioid peptides, *Penk* and prodynorphin (*Pdyn*) and *Oprm1* (Gammie et al. 2016), further supporting the hypothesis that endogenous opioid mechanisms play a role in maternal reward and reinforcement (Nelson and Panksepp 1998).

Summary

In summary, endogenous opioids play key roles in mediating adaptations in the maternal brain. Here the focus was on adaptations in the regulation of the HPA axis, oxytocin system, prolactin system and the circuits governing maternal behaviour. These changes are important for conserving energy, protecting the fetus from harmful levels of maternal glucocorticoids, providing sufficient oxytocin for parturition and lactation, ensuring the onset of parturition occurs in a timely manner and that after birth the offspring are suckled and properly cared for. Appropriate withdrawal of up-regulated central endogenous opioid mechanisms is equally important to support the transition from pregnancy to motherhood.

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Conflict of Interest

The author declares that they have no conflict of interest.

FIGURE LEGENDS

Figure 1 : Anatomical distribution of opioid peptides and receptors in the arcuate, paraventricular and supraoptic nuclei of the rat hypothalamus

The left-hand side of the diagram summarises the distribution of immunoreactivity for dynorphin (dyn), enkephalin (enk) and β-endorphin (βend) in cell bodies (stars) or in neuronal fibres (circles). The right-hand side shows the distribution pattern for mu (μ), delta (δ) and kappa (κ) opioid receptors. For cell bodies (stars) receptors were identified by *in situ* hybridisation; while receptor binding (triangles) was identified by autoradiography. In both cases, the relative expression levels are indicted by the number of a given symbol i.e. one symbol = low; 2 symbols = moderate; and 3 symbols = high expression. 3V, 3rd ventricle; Arc, arcuate nucleus; OT, optic tract; PVN, paraventricular nucleus; SON, supraoptic nucleus. Based on data from: (Abe et al. 1987; Beaulieu et al. 1996; Desjardins et al. 1990; Fallon and Leslie 1986; Khachaturian et al. 1983; Khachaturian et al. 1982; Mansour et al. 1994a; Mansour et al. 1994b; Mansour et al. 1994c; Mansour et al. 1987; Merchenthaler et al. 1986; Minami et al. 1994; Wamsley et al. 1980).

Figure 2: Endogenous opioid inhibition of CRH/oxytocin neurones in late pregnancy

Noradrenergic (NAergic) A2 neurones in the nucleus tractus solitarii (NTS) of the brainstem project to parvocellular corticotropin-releasing hormone (CRH) and magnocellular oxytocin (OT) neurones in the paraventricular nucleus (PVN). In non-pregnant rats, stress (e.g. interleukin-1β, forced swimming) activates these noradrenergic A2 neurones triggering noradrenaline (NA) release from the nerve terminals in the PVN. Noradrenaline acts via α1 adrenoceptors (α1R) to stimulate (+) the CRH/OT neurones, resulting in CRH release at the median eminence (ME) and OT release from the posterior pituitary (PP). In late pregnancy, systemic interleukin-1β fails to stimulate noradrenaline release in the PVN (despite similar activation of the noradrenergic cell bodies in the NTS); hence the CRH and OT neurones are less excited and ACTH/corticosterone and OT secretion is markedly suppressed (↓) or completely absent. This is a consequence of increased inhibition (-) by a central endogenous opioid mechanism. It is proposed that enkephalin (enk) acts presynaptically on up-regulated MOR on the noradrenergic terminals to inhibit stimulated noradrenaline release, since the NTS A2 neurones display increased (↑) expression of proenkephalin-A and MOR mRNA in late pregnancy and infusion of the opioid receptor antagonist naloxone directly into the PVN restores IL-1β-evoked noradrenaline release in the PVN. Moreover naloxone activates the CRH and oxytocin neurones leading to increased ACTH, corticosterone and oxytocin secretion into the blood.

Figure 3: Endogenous opioid control of TIDA neurones in late pregnancy

In virgin rats prolactin secretion is under tonic inhibition (-) by dopamine (DA) secreted by tubero-infundibular dopamine (TIDA) neurones in the arcuate nucleus and secreted into the portal blood system to act on dopamine D2 receptors expressed on lactotrophs in the anterior pituitary. Prolactin acts via prolactin receptors (PRL-R) on TIDA neurons to stimulate (+) dopamine release, producing a short-loop negative-feedback system. Endogenous opioids inhibit TIDA neurones and hence stimulate prolactin secretion; this facilitates the surges in prolactin secretion in early pregnancy and pre-partum. Enkephalin (enk) is markedly up-regulated (↑) in arcuate nucleus TIDA neurones in late pregnancy and it is proposed that enkephalin released from TIDA neurones acts on μ-/κ-opioid receptors to inhibit the dopamine neurones and hence dopamine release (possibly via auto-inhibition). Dynorphin (dyn) containing nerve terminals also make contact with arcuate TIDA neurones and dynorphin acts via κ-opioid receptors to inhibit TIDA neurones. In addition, before parturition, the TIDA neurones become insensitive to negative feedback by prolactin and placental lactogen (PL). These adaptations permit a state of hyperprolactinemia to develop which supports lactation and promotes maternal behaviour.

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Figure 1

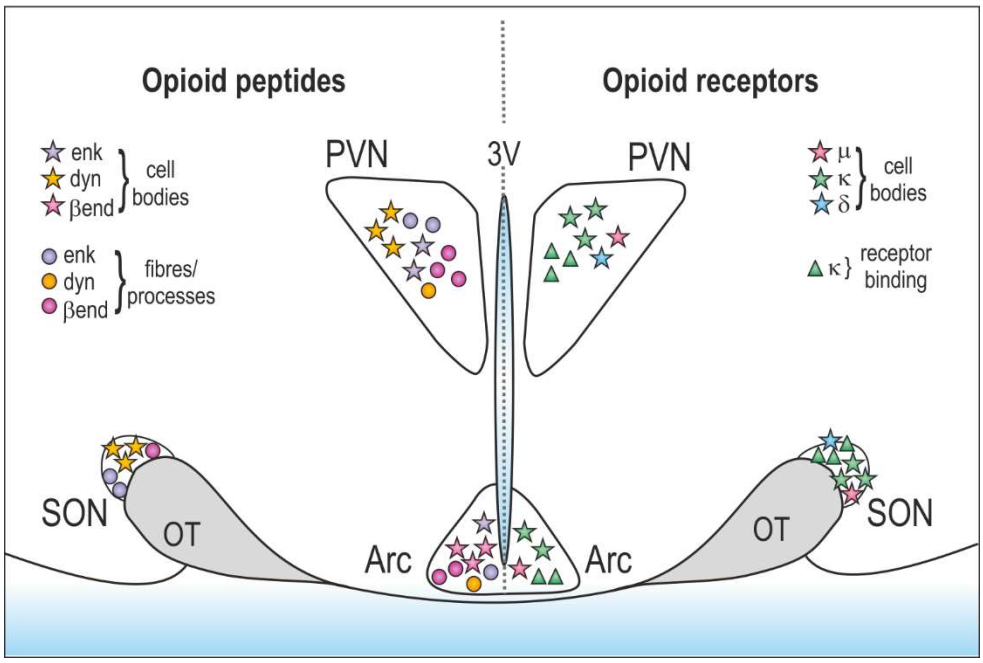
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Figure 2

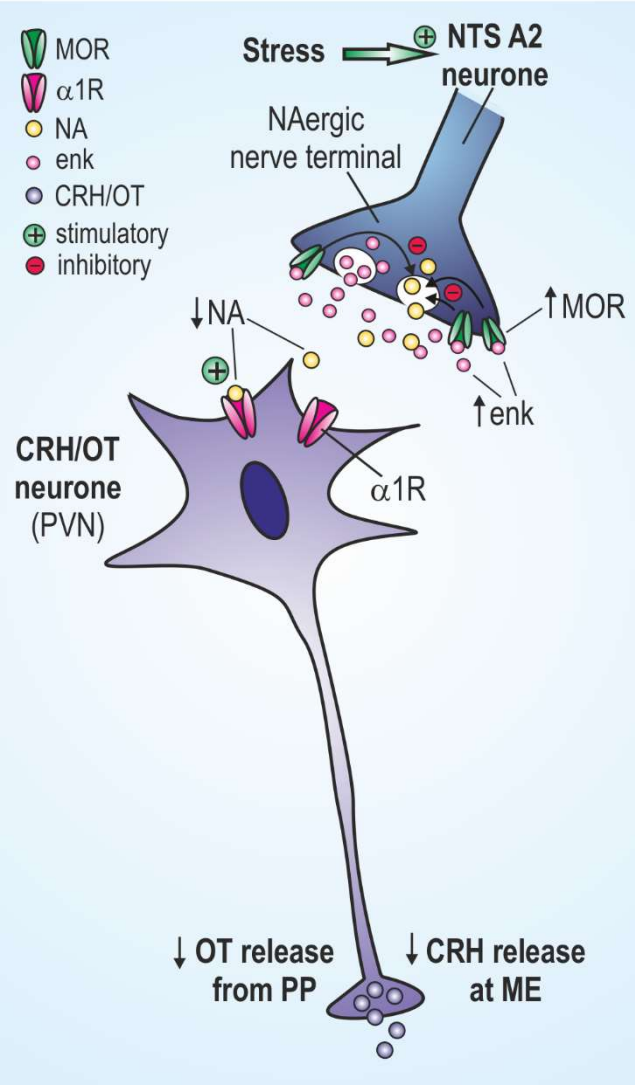
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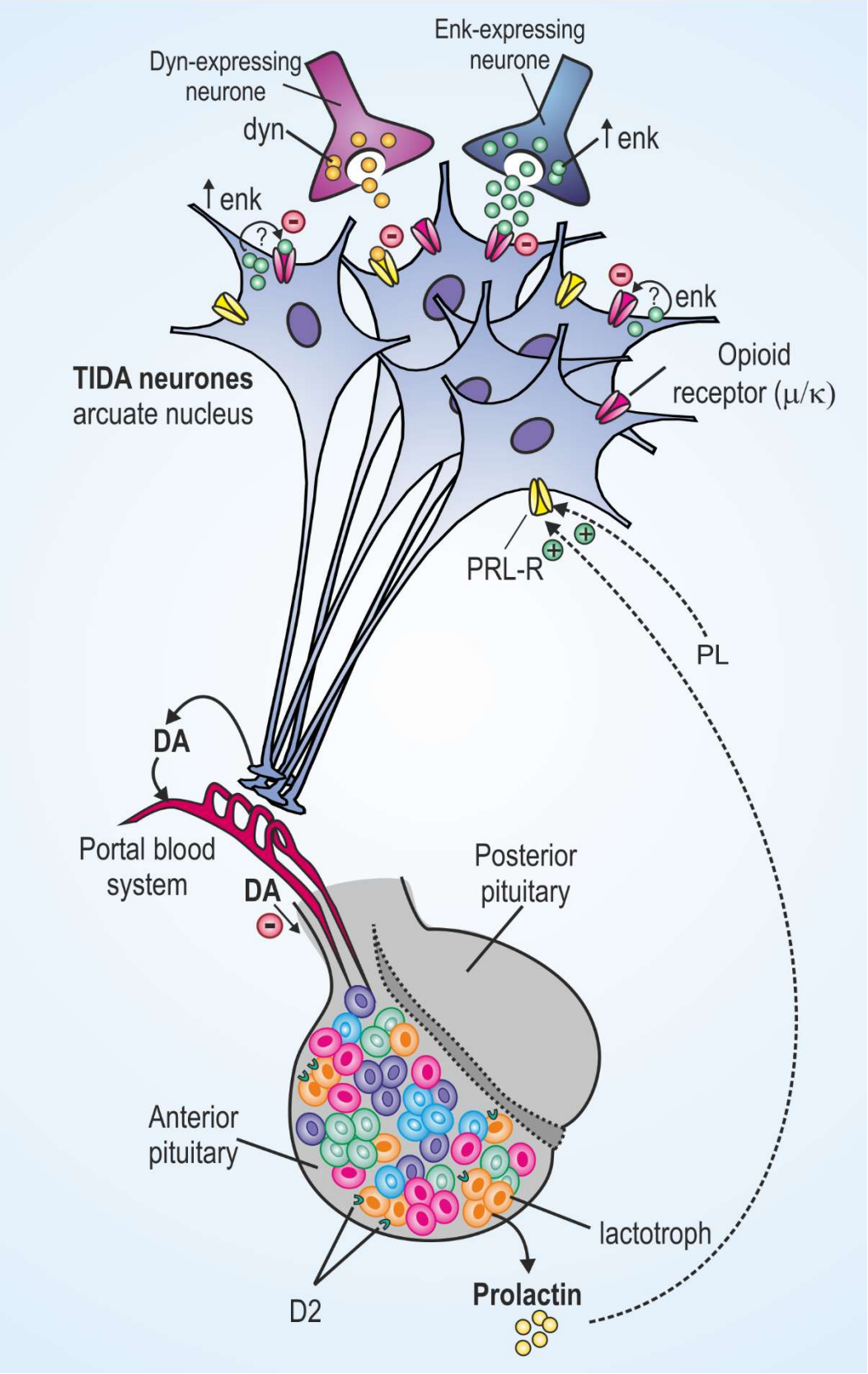
Figure 3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